Comm CARDIOVASCULAR #123317

Dr. Bing
Dr. Jacobson
Dr. Sommers

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N.Y. 10022
(212) 421-8985

Application for Research Grant
(Use extra pages as needed)

Date 7-17-73

1. Principal investigator (give title and degrees).

A. Stanley Weltman, Ph.D., Associate Professor in Pharmacology and Research

2. Institution & address

Laboratories for Therapeutic Research
Research Institute of the Brooklyn College of Pharmacy
Brooklyn College of Pharmacy
Long Island University
600 Lafayette Avenue Brooklyn, N.Y. 11216

3. Department(s) where research will be done or collaboration provided

a) Laboratories for Therapeutic Research
b) Institute of Pathology, Downstate Medical Center, S. U. N. Y.
Brooklyn, N. Y.

4. Short title of study

Effects of Nicotine on Blood Pressure, Blood Lipid Profile, Endocrine Activities and Pathology of Spontaneously Hypertensive and Normotensive Rats

5. Proposed starting date.

January 1, 1974

6. Estimated time to complete.

two years

7. Brief description of specific research aims:

The proposed investigation is being submitted to continue our previous research, "Acute and Chronic Effects of Nicotine and Pathology in Spontaneously Hypertensive and Normotensive Male Rats," awarded under CTR Grants 833; 833R1. Furthermore, an additional goal of the investigation is a detailed study of the plasma lipid profile (cholesterol, FFA, triglycerides, phospholipids) in test and control spontaneously hypertensive and normotensive rats. Initially, the investigation sought to determine possible synergistic and cumulative hypertensive or hypotensive effects contributed by acute subcutaneous and chronic (oral) administration of nicotine to a genetically selected strain of spontaneously hypertensive rats (SHR) and a normotensive strain of Wistar rats (NR). It was anticipated that the study of various biochemical, physiological and morphological differences in treated and untreated hypertensive and normotensive animals sacrificed at various age levels would contribute further knowledge of plasma cholesterol, FFA, Na^+, K^+ and glucose metabolism and regulation as well as evidence of endocrine relationships to hypertension. Consequently, biochemical evaluations have included plasma corticosterone, adrenal corticosterone, adrenal catecholamines (epinephrine, norepinephrine and total catecholamines), plasma glucose, FFA, total plasma proteins, plasma Na^+ And K^+ levels and urine assays of 17-ketosteroid titers (androgens).

An additional objective was and is to determine via detailed macroscopic and histological examinations the gradual etiological and progressive development of cardiovascular and related pathologies in the spontaneously hypertensive

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8. Brief statement of working hypothesis:

Since the present investigation encompasses manifold aspects, the proposal primarily intended to determine the relationship and possible mechanisms via which nicotine may induce hypertension and/or hypotension during acute and/or prolonged administration of the drug. Thus, the investigation attempted and intends to explore alterations in various hormonal titers and biochemical parameters to determine the role of nicotine and hormones on blood pressure levels as well as certain aspects of carbohydrate, fat and salt metabolism and regulation, etc. Thus, biochemical (adrenal catecholamine and corticosterone and plasma corticosterone, glucose, cholesterol, FFA, total protein, and Na^+ and K^+ levels and urinary 17-ketosteroids) as well as organ weights and histological preparations will be measured to ascertain adrenomedullary, glucocorticoid, mineralocorticoid and perhaps gonadal (urinary 17-ketosteroid) role on blood pressure regulation due to nicotine.

To date, testing of male spontaneously hypertensive and normotensive rats (Wistar strains) in an unanesthetized state with 2.28 mg/kg of nicotine alkaloid per day have not revealed a biphasic effect as reported by Wenzel et al (31,32) with anesthetized female Sprague-Dawley rats (normotensive). Since Wenzel et al (32) reported hypotensive effects with higher doses in the normotensive Sprague-Dawley rats, the question arises whether male Wistar rats are more susceptible to equivalent

(see attached sheet p.11)

9. Details of experimental design and procedures (append extra pages as necessary)

Five week old immature male rats of the spontaneously hypertensive strain (SHR) developed by Okamoto and Aoki (14) and normal(NR)Wistar rats (Carworth, Inc.) will be obtained from appropriate breeding laboratories. Hypertension is usually observable at 2 months of age in the SHR (20). Upon arrival all animals will be weighed on a Torbal Balance and carefully examined for signs of physical disability and ill-health. All rats will be housed in plastic cages (9"x11"x15") in groups of 4 rats per cage and weighed at weekly intervals. The animals will be permitted to acclimate for a 1 week period and will be supplied with Purina Lab Chow for food and permitted to drink water ad libitum. To determine the progressive development of spontaneous hypertension in the SHR rats, systolic blood pressure will be measured in the SHR groups as well as the normotensive rats (NR) at 6, 9, and 11 week age periods. The indirect tail-cuff method using the Narco-Biosystems Physiograph (Desk Model DMP-4B) will be used on unanesthetized rats for the systolic blood pressure measurements. Each rat will be prewarmed in an incubator for 15 minutes at 35 C prior to transfer to a Narco-Biosystems rat holder-warming unit (37 C).

At the completion of the 3 preliminary blood pressure readings, rats of each of the spontaneously hypertensive and normotensive groups will be matched according to systolic blood pressure and body weight for separation into appropriate test and control SHR and NR groups (4 groups).

Commencing at 11 weeks of age after determination of base-line systolic blood pressures, nicotine alkaloid (Eastman Kodak) will be administered subcutaneously, twice daily at 9:00 A.M. and 4:00 P.M. The dose will be divided to ensure that the total dosage approximates 2.28 mg/kg/day. This has been calculated to be equivalent to 2 packs of cigarettes/day. On week-ends, oral administration procedures will be used by supplying drinking water containing appropriate doses of nicotine alkaloid based on water consumption measurements. When injected subcutaneously, the nicotine will be administered in the form of a slow absorption and releasing aqueous vehicle by dissolving the appropriate nicotine concentrations in a sterile 2% glycerin - 2% gelatin preparation. Control spontaneously hypertensive and normotensive rats will receive corresponding injections of the 2% glycerin - 2% gelatin preparations.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

a) The space and facilities available at the Laboratories for Therapeutic Research, Brooklyn College of Pharamcy are as follows:

The Laboratories were designed for the purpose of conducting animal investigations in physiology, pharmacology, endocrinology, biochemistry, and experimental therapeutics. It is a Laboratory which is equipped for work in all of these fields and possesses histological, microscopic, biochemical and animal-surgical equipment necessary for the conduct of detailed investigations.

The animal rooms are air-conditioned, the animals are housed in metal cages and an automatic cage-washing machine is available. The permanent equipment in addition to the cages includes: (1) Leitz Ortholux Binocular Microscope, (1) Sartorius Selecta Precision balance, (1) F.P.E. Precision balance, (2) ovens, (2) Incubators, (2) Refrigerators, (1) Freezer, (1) Turner Fluorometer, Model 110, (1) Coleman Spectrophotometer, Model 6, (1) Spectronic 20 (Bausch & Lomb), (1) Servall Centrifuge, (1) Adams Dynac Centrifuge, (1) Torbal Torsion Balance, (1) Bausch and Lomb freezing and (1) Spencer rotary paraffin microtome, a Technicon for processing histological specimens, (1) Beckman pH Meter, (2) A.H. Thomas shakers, (1) Demineralizer Unit (Barnstead), (1) Corning AG-1 Glass Distilling Apparatus, (1) Hot plate, (1) Stir-Jack, (1)Elconap Constant Temperature Water Bath, (1) Friden Calculator, (1) Friden 130 Electronic Calculator, (1) Marchant Cogito 566 PR Calculator, (1) General Radio Oscillator, Type 1210 C and amplifier, (1) Audiogenic-Stress Belling Chamber, (1) Stainless Steel Pipette Washer and a miscellany of glassware and accessory equipment. (1) Narco-Biosystems, Desk Model DMP-4B, Physiograph and accessory equipment for systolic blood pressure measurements.

The animals are housed in an air-conditioned room approximately 22' x 27' (594 sq. ft.), provided with an exhaust system, which can contain 8-9 animal racks. Cages for mice or rats are available depending upon the particular study. The animal room contains water facilities and a drainage system for proper sani-

(see attached sheet page 19)

11. Additional facilities required:

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12. Biographical sketches of investigator(s) and other professional personnel (append):

A.S.Weltman (pages 21-24), V.M. Yermakov (pages 25-27), S. Schwan (pages 28-29)

13. Publications. (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

see p. pg. 30

Source: https://www.industrydocuments.ucsf.edu/docs/kpvm0000

R: REDACTED MATERIAL

14. First year budget:

A. Salaries (give names or state "to be recruited")	% time	Amount
Professional (give % time of investigator(s) even if no salary requested)		
A. Stanley Weltman, Ph.D.	25	
Valentin M. Yermakov, M.D.	10	
Stefan Schwan, M.D.	25	REDACTED
Technical		
Vijay Pandhi, M.S.	100	
Leroy Johnson, B.S.	100	
Ratilal Vaidya	50	REDACTED
Caretaker	30	
Pathology Technician	100	
Sub-Total for A		

B. Consumable supplies (by major categories)

Wistar and Spontaneously Hypertensive Rats	1250
Feed and Bedding	1100
Glassware, Chemicals, Recording Physiograph Paper, Linens, etc.	1350
Pathology-Technical stains, slides, chemicals, etc.	5000
	8700
Sub-Totall for B	

C. Other expenses (itemize)

Publications	200
Sub-Total for C	200
Running Total of A + B + C	REDACTED

D. Permanent equipment (itemize):

Thin Layer Chromatography Apparatus (Tanks; U.V. Lamp; Plates; etc.	900
Flame Photometer (Coleman #21; NA and K)	750
Furnace, Ashing Oven and Temperature Control	650
Sub-Total for D	2300
E	7316
Total request	REDACTED

E. Indirect costs (15% of A+B+C)

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	REDACTED	$9200	$200		$8010	REDACTED
Year 3						

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16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Laboratories for Therapeutic Research Research Institute of The Brooklyn College of Pharmacy, is a non-profit basic research institution at Brooklyn College of Pharmacy. Costs of Plant Operation are jointly shared by the College and the Laboratories. Expenses for the Laboratories Operation are from private contributions.			

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

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It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name A. Stanley Weltman, Ph.D

Signature A. Stanley Weltman Date 7/16/73

Telephone 212 (Area Code) MA 2-1790 (Number) (Extension)

Checks payable to

Brooklyn College of Pharmacy

Mailing address for checks

600 Lafayette Ave., Brooklyn, N.Y. 11216

Responsible officer of institution

Typed Name Seymour Schertz

Title Comptroller

Signature Seymour Schertz Date 7/16/73

Telephone 212-MA2-4040 (Area Code) (Number) (Extension)

Source: https://www.industrydocuments.ucsf.edu/docs/kpvm0000

Item #7. Brief Description of Specific Research Aims

and normotensive rats as related to age and prolonged nicotine administration. Histological preparations and examinations of the heart, aorta, pulmonary artery, renal blood vessels, mesenteric blood vessels, brain, lungs, fundus of the eye, lungs, kidneys, testes, liver, spleen, thymus, pituitary and pancreas have and will be used to determine the extent of associated cardiovascular pathology and endocrine involvements in the respective organs. The frequency and extent of cardiac infarctions (scarring and hypertrophy), periarteritis nodosa, nephrosclerosis, cerebral and lung pathologies will be carefully assayed. Thus, this intensive biochemical, endocrine and histological study associated with repeated measurements of systolic blood pressure and body growth should aid in determining the degree of pathological involvements and nicotine-related effects in spontaneously hypertensive and normotensive rats. This investigation should aid in clarifying present day inconsistencies and ambiguities concerning possible harmful, neutral or beneficial influence of nicotine intake to man and its possible involvement with essential hypertension. Of added import, the recent findings of significant decreases in total cholesterol levels in 6 and 29 week studies (oral, 2.28 mg/kg/day of nicotine alkaloid) in the spontaneously hypertensive test rats merit further investigation regarding the effects of nicotine on the blood lipid profile.

Various investigators have reported no apparent increased activity in the renin-angiotensin system of the SHR strain (90, 91). Additional research have likewise indicated no evidence that the renal humoral pressor system of the SHR was hypereactive (92) or that renin was increased in the SHR (76). Others have reported that the SHR seem to be hyperresponsive to the hypertensive-inducing effects of rat kidney extracts (93). During the investigation, procedures will be attempted to assess the possible effect of nicotine on the renin-angiotensin system of the spontaneously hypertensive and normotensive strains.

The habit of smoking tobacco has long been suspected and accused of being an etiological factor leading to cardiovascular diseases (hypertension, arteriosclerosis, artherosclerosis, etc.) (1-11). Epidemiological and statistical studies have claimed a greatly increased risk of coronary heart disease, morbidity, and mortality from cardiovascular disease in smokers than in non-smokers (12, 13).

In recent years (14) a strain of spontaneously hypertensive rats (SHR) has been selectively bred, which various investigators consider to be most appropriate for studies relative to essential hypertension (14-16). Various extirpative, as well as exogenous hormone procedures have been used to demonstrate and test the active role of the pituitary-adrenal axis and pituitary-thyroidal role in inducing and maintaining the hypertensive state in the SHR strain (17, 18). Other investigations have demonstrated the contributing role of the adrenal medullary activity and catecholamine output with the development of the spontaneously hypertensive state (19-21). Evaluation of pathological changes in blood vessels, heart, kidneys, brains, etc. of the spontaneously hypertensive rats (22) have paralleled changes found in cardiovascular diseases and essential hypertension in man.

Considerable epidemiological and pathological studies have been devoted to determine effects and association of tobacco smoking to emphysema, chronic bronchitis, cardiovascular diseases and lung cancer (4, 7). It has been cited statistically that heavy smokers have higher mortality rates from coronary heart disease than non-smokers (4). Whether the habit of smoking tobacco can be related to the development of hypertension and coronary diseases has, thus, long been the subject of much discussion (4, 7)

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Item #7. Brief Description of Specific Research Aims

In doses absorbed by cigarette smokers during and shortly after smoking, nicotine has been found to increase heart rate, raise arterial pressure, dilate arterial blood vessels of muscles, while contracting those of the skin, increase cardiac output (9) and reduce the skin temperature of the extremities (23). Nicotine, thus, produces a complex array of cardiovascular responses and hemodynamic effects in which the precise mechanisms cannot be readily defined (24). In considering the pharmacological actions of nicotine, low doses stimulate the sympathetic ganglia, aortic and carotid chemoreceptors and catecholamine release from the adrenal medulla which can cause increased blood pressure and heart rate changes (25). Large doses block ganglionic transmission. In addition, nicotine also stimulates ganglia of the parasympathetic system and the pulmonary and coronary arterial receptors which induce lowering in blood pressure and heart rate values (25).

It is evident from smoking studies in man (5, 23) and animals (26, 27) that acute tobacco smoke and/or nicotine produce transient increases in blood pressure, etc. In epidemiological studies of tobacco smoking effects, Hadley (28) reported that the average blood pressure of smokers was somewhat less than non-smokers. Hammond and Horn (29) and Damon (7) were unable to establish a relation between cigarette smoking and hypertension. Blackburn, et al. (1) also reported lower distinct tendencies of systolic and diastolic blood pressure in chronic smokers but found higher basal pulse rates and resting pulse rates in smokers. Smoking has also been reported to cause larger rises in blood pressures of hypertensive subjects than in normal subjects (3).

Chronic studies with animals involving effects of nicotine on blood pressure have also been inconsistent. In part, these inconsistencies may be related to differences in species, strain, sex, dose, mode of administration, blood pressure procedures etc. Haag et al. (26) exposing rats to chronic cigarette smoke for 2 years reported that tobacco smoke did not produce significant differences in blood pressure, evidence of hypertension but reported tendencies of lower blood pressure values towards the end of the study. In contrast, rabbits administered nicotine alkaloid in drinking water revealed significant and cumulative increases in systolic blood pressure from 0 - 24 weeks (30). However, with famale rats Wenzel et al. (31) reported that chronic oral administration for 55 weeks with a nicotine dose of 2.28 mg/kg/day equivalent to 2 packs of cigarettes per day exerted a biphasic effect on blood pressure. Initially systolic blood pressure readings of anesthetized rats showed gradual increases up to 20 weeks followed by subsequent depressor effects on blood pressure upon continued nicotine administration. Larger oral doses (3.44 and 4.56 mg/kg/day), however, induced only depressor or hypotensive effects on the systolic blood pressure levels (32). Administration of either the "low" or "high" oral doses of nicotine alkaloid to renal hypertensive rats lowered systolic blood pressures to below control levels once renal hypertension was established (32). Bhagat (33) administering nicotine subcutaneously for 6 weeks and Westfall (34) for 8 weeks to rats reported gradual and significant increases in systolic blood pressures.

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Item #7. Brief Description of Specific Research Aims

There have been conflicting reports regarding the association of smoking with blood cholesterol levels. Several investigators (7,35) have reported higher values in smokers, but Blackburn et al. (1) did not observe a statistically significant difference. Others (36, 37) have reported a statistical relationship between cigarette smoking and elevated serum lipids. Kershbaum et al. (38, 39) has demonstrated that free fatty acids are rapidly mobilized in man and dogs after cigarette smoking or nicotine administration. These changes resulted from the nicotine stimulated secretion and release of adrenal catecholamines (40). The possibilities of heightened levels of blood cholesterol, lipids and free fatty acids due to smoking or nicotine have significance in view of claims of direct relationships between smoking and atherosclerosis. Moreover, it has been reported that rabbits fed a cholesterol diet and administered nicotine showed an increase in serum cholesterol and the degree of aortic atherosclerotic lesions (41). It should be noted that Kershbaum et at. (8) reported significant increases in the serum cholesterol levels of dogs administered nicotine for 6 weeks but no significant changes in triglyceride levels. However, Wenzel and Beckloff (42) reported that rabbits administered nicotine and fed a minimal (0.1%) cholesterol diet showed significant increases in both plasma cholesterol and phospholipid.

Other biochemical investigations have similarly been diverse. Whereas, Blackburn et al. (1) reported higher fasting blood sugar levels in smokers, Roth and Schick (3) claimed that fasting blood sugar levels did not rise appreciably after and during smoking. Milton (43) has reported that low doses of nicotine considered to be in the smoking range increased blood sugar and mobilized non-esterified fatty acids in cats due to increased catecholamine secretions. The possible involvement of other hormonal systems must however be considered in relation to glucose metabolism and the carbohydrate metabolic processes. Thus plasma glucocorticoid output (acute study) which also controls carbohydrate metabolsim was stimulated probably as a secondary effect of catecholamine release. Recent reports (44) have also cited the "high" concentrations of nicotine inhibit glucose-induced insulin secretion, while "lower" doses stimulate insulin secretion. Our histological study of the pancreas should probably evaluate the effect of nicotine on this endocrine gland.

To date, as indicated in accompanying progress reports etc., acute administration of nicotine to the spontaneously hypertensive rats stimulated adrenocortical (corticosterone) and adrenomedullary (catecholamine) release along with mobilization of FFA and increased glucose and cholesterol levels responses probably due to increased catecholamine output. One questions whether the significant depletion noted in K+ (76) levels by the larger dose at 30 minutes and both doses at the 1 hour interval may possibly be the result of a nicotine-induced release of mineralocorticoid hormones.

Evaluation of the effects of prolonged administration (6 weeks and 29 weeks) revealed in general no evidence of pronounced or restrained hypertensive effects on systolic blood pressures of the nicotine treated spontaneously hypertensive rats. In contrast, the SHR group showed consistent trends of hypotensive effects which at times were statistically significant during the 29 week oral administration period.

In general, oral nicotine administration showed pronounced decreases in the body weights of the treated spontaneously hypertensive and normotensive rats.

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Item #7. Brief Description of Specific Research Aims

As indicated in the progress report, both the test SHR and NR groups revealed significant increases in the relative adrenal weights (29 week study). No consistent findings were observed in the other relative organ weight analyses. It is evident that the test spontaneously hypertensive rats (6 and 29 week studies) showed significant decreases in plasma cholesterol levels but no comparable alterations in plasma FFA titers. A trend of similar decreases in the cholesterol levels of the test normotensive rats after 29 weeks of treatment was not significant. After 29 weeks, significant decreases were observed in the plasma glucose levels of the nicotine treated normotensive rats but smaller decreases in the SHR group were not statistically significant. One questions the possible differential effects of nicotine on the regulation of adrenocortical, adrenomedullary and insulin secretory processes in the spontaneously hypertensive and normotensive rats.

The following investigation therefore has several continuing objectives:

1. To further study possible differential effects of prolonged administration of nicotine on systolic blood pressure responses of spontaneously hypertensive and normotensive rats.

2. By various biochemical, organ weight and histological procedures to evaluate differential effects of nicotine on adrenocortical (glucocorticoid and mineralocorticoid)adrenomedullary (catecholamine), gonadal (17-ketosteroid etc.), and the pancreatic hormonal systems of the hypertensive and normotensive rats and their relationships to the possible development of hypertension and pathology.

3. As a result of significant decreases in the plasma cholesterol levels of the spontaneously hypertensive rats, to initiate a complete blood lipid profile study of the effects of nicotine in the SHR and normotensive strains. This would include plasma cholesterol (free and total), plasma FFA, triglyceride and phospholipid levels in addition to evaluating the comparative effects of nicotine on the amounts of stored body fats. In view of the oft-cited relationship of high blood cholesterol and lipid levels to the development of hypertension and artherosclerosis, etc., this aspect should be of significant import.

4. An additional continuing aim is to determine via macroscopic and histological observations the gradual etiological and progressive development of cardiovascular and related pathologies in the spontaneously hypertensive and normotensive rats either related to age or administration of nicotine.

The present investigators have published investigations with hallucinogens such as lysergic acid diethylamide (45-49) and mescaline (50-54) on the metabolism behavior and endocrine function of rats and mice.

Our Laboratory has also engaged in studies related to the effects of auditory stress (55-57), vibration stress (58-60), isolation stress (61-65) as well as behavioral, metabolic and physiological differences in audiogenic-seizure suseptible vs. resistant rats (66-68) and the excitable homozygous-whirler vs. normal, heterozygous-whirler mutant mice (69-75). The various behavioral, biochemical and endocrine studies have indicated heightened metabolism rates, increased adrenocortical function and, in general, inhibited gonadal activity in the whirler mice. These may be symptomatic and correlated with physiological and neuronal changes responsible for the wild, circling, locomotor activity. Biochemical alterations have indicated significantly increased plasma corticosterone (72,73), adrenal corticosterone (72, 73) and adrenal catecholamine levels (73)

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Item # 7. Brief Description of Specific Reeerch Aims

As indicated in the progress report, both the SHR [illegible] accompanied by significant alterations in carbohydrate metabolism (72,73,75) (i.e., lower plasma glucose and liver glycogen levels). Although total plasma protein levels were significantly reduced due to depressions in $\alpha 1$, $\alpha 2$, beta and gamma globulins, albumin levels were significantly higher (72).

In the budget for permanent equipment etc., we have listed items such as thin layer chromatography and furnace-ashing oven apparatus. If these items are granted, the TLC equipment plus our existing tools will enable us to determine plasma and adrenal disoxycorticosterone levels for assay of mineralocorticoid output in the nicotine treated and control spontaneously hypertensive and normotensive animals.

In addition, the TLC equipment will enable us to extract and assay nicotine and metabolites of nicotine, i.e. cotinine from the treated animals.

The ashing oven will enable us to do PBI studies and measure thyroid function and activity in the test and control SH and normotensive groups.

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Item #8. Brief Statement of Working Hypothesis

doses of nicotine than the Sprague-Dawley strain. Nicotine lowered the blood pressure readings of Sprague-Dawley renal hypertensive rats (32).

The capacity of nicotine to diversely effect blood pressure via the sympathetic and/or parasympathetic system, certain vascular chemoreceptors, and/or ganglionic blockade renders it difficult to completely differentiate between neurogenic and hormonal mediating influences on blood pressure regulating mechanisms.

Correlative studies of alterations in plasma glucose, Na^+ and K^+ as well as a detailed assay of the blood lipid profile (cholesterol, FFA, triglycerides and phospholipids) at various time and age periods should contribute knowledge concerning the fundamental basis and development of essential hypertension, cardiovascular diseases and associated pathologies, etc.

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Item #9. Details of Experimental Design and Procedures

The effects of nicotine on systolic blood pressure, body weights, biochemical parameters, endocrine function and cardiovascular pathologies, etc. will be studied in test and control groups of 4 age levels (4 weeks, 6 months, 1 year and 1½ years). Body weights will be measured weekly and food consumption of aliquot groups will be recorded weekly. Blood pressure readings of the respective test and control experimental groups will be recorded after the first and 2nd weeks of nicotine administration and on alternate weeks thereafter.

At appropriate intervals prior to sacrifice urine collections will be obtained from the test and control spontaneously hypertensive and normotensive groups to evaluate urinary 17-ketosteroid (77) and urinary catecholamine (78) output. The following schema presents the format and population sizes of the various experimental studies:

Protocol: Four groups of SHR and NR to be sacrificed after 4 weeks, 6 months, 1 year and 1½ years of nicotine alkaloid administration (subcutaneously, twice daily in slow release preparations; dose 2.28 mg/kg/day.

Group I: 4 weeks	Test SHR-	30 rats
	Control SHR-	30 rats
	Test NR-	30 rats
	Control NR-	30 rats
	Total-	120 rats

Group II (6 months), Group III (1 year) and Group IV (1½ years) to consist of larger initial populations (35 per group) to compensate for experimental deaths. Total rats for the 4 groups-480 rats.

During the course of the respective experimental investigations at appropriate intervals, test and control SHR and NR will be sacrificed by rapid decapitation (Harvard decapitator) and blood samples will be collected in heparinized beakers for plasma corticosterone (79) glucose (80), total protein (81) and Na^+ and K^+ (82) assays. In addition, aliquot plasma samples will be analyzed for total cholesterol (83) and free cholesterol (83), plasma FFA (84), triglyceride (85) and phospholipid (86) titers. The adrenals will be rapidly excised, trimmed of fat and connective tissue and weighed prior to adrenal corticosterone (87) and adrenal catecholamine (88) analyses. Thus, the various biochemical tests associated with organ weights and histological data will furnish information concerning the responsiveness and differential effects of nicotine on the spontaneously hypertensive and normotensive rats. The assays will yield insight into adrenomedullary (catecholamine), adrenocortical (glucocorticoid and mineralocorticoid) and possibly gonadal (androgenic 17-ketosteroids) and the hormonal influences on glucose, fat and Na^+ and K^+ metabolic and regulatory processes, etc. Histological preparations of the pancreas and pituitary will yield further information concerning their respective hormonal products.. During the various autopsy periods care will be exercised to check for gross pathologies and to approximate amounts of intradermal fat in the respective test and control groups. Such organs as the adrenals, heart, liver, spleen, thymus, kidneys, testes, seminal vesicles, lungs and brain will be removed for organ weight analyses, in addition to being checked for gross pathology. All organs will be weighed on a Sartorius Selecta

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Item #9. Details of Experimental Design and Procedures

Balance to the nearest 0.1 mg. Histological preparations will be made of the heart, aorta, pulmonary artery, renal blood vessels, mesenteric blood vessels, testes, liver, lungs, brain, eye, pancreas, and pituitary to determine the extent and presence of either associated cardiovascular pathologies, hormonal functions and possible effects of nicotine administration in the SHR and NR groups.

Based on gross and microscopic observations, the animals will be examined for cardiac infarctions (scarring and hypertrophy), periarteritis nodosa, nephrosclerosis, cerebral hemorrhage, lung involvement, etc.

Depending upon specific requirements, tissues and organs will be fixed in 10% formalin or Bouin's fixative and stained after sectioning with hematoxylin and eosin or corresponding appropriate stains (i.e. van Gieson's strain, elastic-van Gieson's stain, PAS stain and elastic-PAS stain, fat stains, etc.).

All blood pressure, biochemical, organ weight, etc. data will be analyzed for statistical significance by standard t test and variance procedures (89) whenever appropriate. Correlation procedures (89) will be used to analyze i.e., cholesterol and blood pressure values, etc., to determine the direct or inverse relationships of the various biochemical parameters with hypertension or nicotine administration. The laboratory has available a Cogito 566 PR model calculator (Marchant) as well as a Friden 130 Electronic Calculator for computation of the data. In addition, the laboratories has available, the facilities of the Long Island University, Brooklyn Center, Computer Center. The Computer Center has an IBM Model No. 1130-3C computer and accessories available for the statistical analyses.

Thus, this detailed biochemical, endocrine, histological and pathological series of investigations should aid in determining short and long range effects of nicotine on physiological and hormonal processes of spontaneously hypertensive and normotensive rats. The investigation should aid in clarifying present inconsistencies and ambiguities concerning nicotine in relation to blood pressure, blood lipid profile, etc., and their pathological implications. This study should possibly resolve questions concerning harmful, neutral or beneficial aspects of nicotine intake to man and perhaps yield information pertinent to essential hypertension.

1003541965

Source: https://www.industrydocuments.ucsf.edu/docs/kpvm0000

REFERENCES

1. Blackburn, H., Brozek, J., Taylor, H. L. and Keys, A.: Ann. N. Y. Acad. Sci. 90:277, 1960.
2. Hines, E. A.: N. Y. Acad. Sci. 90:333, 1960.
3. Roth, G. M. and Schick, R. M.: Ann. N. Y. Acad. Sci. 90:308, 1960.
4. Thomas, C. B.: Ann. Int. Med. 53:697, 1960.
5. Thomas, C. B. and Murphy, E. A.: Ann. N. Y. Acad. Sci. 90:266, 1960.
6. von Ahn, B.: Ann. N. Y. Acad. Sci. 90:190, 1960.
7. Damon, A.: Science 134:339, 1961.
8. Kershbaum, A., Billet, S. and Khorsandian, R.: Amer. Heart J. 69:206, 1965.
9. Kerrigan, R., Jain, A. C. and Doyle, J. T.: Amer. J. Med. Sci. 255:133, 1968.
10. Kershbaum, A. and Billet, S.: Geriatrics 21:155, 1966.
11. Auerbach, O., Hammond, E. C. and Garfinkel, L.: New Eng. J. Med 273:775, 1965.
12. Hammond, E. C. and Horn, D.: J. A. M. A. 155:1316, 1954.
13. Doyle, J. T., Dawber, T. R., Kannel, W. B., Kinch, S. H. and Kahn, H. A.: J. A. M. A. 190:886, 1964.
14. Okamoto, K. and Aoki, K.: Jap. Circul. J. 27:282, 1963.
15. Tabei, R., Spector, S., Louis, W. J. and Sjoerdsma, A.: Clin. Pharmacol. Therap. 11:269, 1970.
16. Ebihara, A. and Martz, B. L.: Amer. J. Med. Sci. 259:257, 1970.
17. Aoki, K.: Jap. Heart J. 4:561, 1963.
18. Aoki, K.: Jap. Heart J. 5:57, 1964.
19. Morisawa, T.: Jap. Circul. J. 32:161, 1968.
20. Ozaki, M., Suzuki, Y., Yamori, Y. and Okamoto, K.: Jap. Circul. J. 32:1367, 1968.
21. Louis, W. J., Tabei, R., Spector, J. and Sjoerdsma, A.: Circul. Res. 24:93, 1969, Suppl. I.
22. Okamototo, K., Aoki, K., Nosaka, S. and Fukushima, M.: Jap. Circul. J. 28: 943, 1964.

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REFERENCES

23. Simon, D. L. and Iglauer, A.: Ann. N. Y. Acad. Sci. 90:119, 1960.

24. Puri, P. S., Alamy, D. and Bing, R. J.: J. Clin. Pharmacol. 295:295, 1968.

25. Comroe, J. H., Jr.: Ann. N. Y. Acad. Sci. 90:48, 1960.

26. Haag, H. B., Larson, P. S. and Weatherby, J. H.: Ann. N. Y. Acad. Sci. 90:227, 1960.

27. Armitage, A. K.: Brit. J. Pharmacol. 25:515, 1965.

28. Hadley, H. G.: Med. Rec. 153:267, 1941.

29. Hammond, E. C. and Horn, D.: J. A. M. A. 166:1294, 1958.

30. Wenzel, D. G., Kamal, J. S. and Turner, J. A.: Ann. N. Y. Acad. Sci. 90: 302, 1960.

31. Wenzel, D. G., Wattanapongsiri, A. and Vedral, D.: J. P. E. T. 145:315, 1964.

32. Wenzel, D. G. and Azmek, N.: Arch. Internat. Pharm. Therap. 187:367, 1970.

33. Bhagat, B.: Brit. J. Pharmacol. 38:86, 1970.

34. Westfall, T. C.: European J. Pharmacol. 10:19, 1970.

35. Karvonen, M., Orma, E., Keys, A., Fidanza, F. and Brozek, J.: Lancet 1:492, 1959.

36. Bronte-Stewart, B.: Brit. Med. J. 1:379, 1961.

37. Gofman, J. W., Lindgren, F. T., Strisower, B., DeLalla, O., Glazier, F. and Tamplin, A.: Geriatrie 10:349, 1955.

38. Kershbaum, A., Billet, S., Dickstein, E. R. and Feinberg, L. J.: Circulat. Res. 9:631, 1961.

39. Kershbaum, A., Billet, S., Caplan, R. F. and Feinberg, L. J.: Amer. Cardiol. 10:204, 1962.

40. Kershbaum, A., Khorsandian, R., Caplan, R. F., Billet, S. and Feinberg, L. J.: Circulation 28:52, 1963.

41. Stefanovich, V., Fore, I., Kajiyama, G. and Iwanaga, Y.: Exper. Molecular Pathol. 11:71, 1969.

42. Wenzel, D. G. and Beckloff, G. L.: J. Amer. Pharm. Assoc. Sci. Ed. 47:338, 1958.

10035419 67

Source: https://www.industrydocuments.ucsf.edu/docs/kpvm0000

REFERENCES

43. Milton, A. S.: Brit. J. Pharmacol. 26:256, 1966.

44. Tjalve, H. and Popov, D.: Endocrinol. 92:1343, 1973.

45. Sackler, A. M., Weltman, A. S. and Owens, H.: Nature 198:1119, 1963.

46. Sackler, A. M., Weltman, A. S. and Sparber, S. B.: Nature 199:1194, 1963.

47. Weltman, A. S. and Sackler, A. M.: J. Pharm. Sci. 54:1382, 1965.

48. Weltman, A. S. and Sackler, A. M.: J. Endocrinol. 34:81, 1966.

49. Sackler, A. M., Weltman, A. S. and Owens, H.: Toxicol. Applied Pharmacol. 9:324, 1966.

50. Weltman, A. S., Sackler, A. M. and Schwartz, R.: Amer. Zool. 8:753, 1968.

51. Weltman, A. S., Sackler, A. M. and Schwartz, R.: Exp. Med. Surg. 26:187, 1968.

52. Weltman, A. S., Sackler, A. M. and Schwartz, R., Johnson, L. and Steinglass, P.: Amer. Zool. 9:1079, 1969.

53. Weltman, A. S., Sackler, A. M. and Johnson, L.: J. Pharm. Sci. 59:1659, 1970.

54. Sackler, A. M., Weltman, A. S. and Johnson, L.: Acute Effects of Mescaline HCl on Behavior, Resistance and Endocrine Function of Male Mice. Exp. Med. Surg. 29:118, 1971.

55. Jurtshuk, P., Jr., Weltman, A. S., and Sackler, A. M.: Science 129:1425, 1959.

56. Sackler, A. M., Weltman, A. S., Bradshaw, M. and Jurtshuk, P., Jr.: Acta Endocrinologica 31:405, 1959.

57. Sackler, A. M., Weltman, A. S. and Jurtshuk, P., Jr.: Aerospace Med. 31:749, 1960.

58. Weltman, A. S., Sackler, A. M., Owens, H. and Bernstein, M.: Amer. Zoologist 3:526, 1963.

59. Sackler, A. M. and Weltman, A. S.: Aerospace Med. 37:158, 1966.

60. Weltman, A. S., Sackler, A. M., Gennis, J. and Steinglass, P.: The Physiologist 9:318, 1966.

61. Weltman, A. S., Sackler, A. M., Sparber, S. B. and Opert, S.: Fed. Proc. 21: 184, 1962.

62. Weltman, A. S., Sackler, A. M. and Sparber, S. B.: Aerospace Med. 37:804, 1966.

1003541968

Source: https://www.industrydocuments.ucsf.edu/docs/kpvm0000

REFERENCES

63. Weltman, A. S., Sackler, A. M., Schwartz, R. and Owens, H.: Laboratory Animal Care 18:426, 1968.

64. Sackler, A. M., Weltman, A. S., Schwartz, R. and Steinglass, P.: Acta Endocrinologica 62:367, 1969.

65. Weltman, A. S., Sackler, A. M. and Schwartz, R.: Life Sciences 9:291, 1970.

66. Sackler, A. M., Weltman, A. S., Owens, H., Kreger, A. S. and Jacobs, R.: Amer. Zool. 2:553, 1962.

67. Sackler, A. M., Weltman. A. S. and Kreger, A. S.: Exp. Med. Surgery 24:258, 1966.

68. Weltman. A. S., Sackler, A. M. and Owens, H.: Physiology and Behavior 3:281, 1968.

69. Sackler, A. M., Weltman, A. S., Steinglass, P., and Kraus, S. D.: Fed. Proc. 23:252, 1964.

70. Weltman, A. S. and Sackler, A. M.: Proc. Soc. Exp. Biol, Med. 123:58, 1966.

71. Sackler, A. M. and Weltman, A. S.: Jour. Exp. Zool. 164:133, 1967.

72. Weltman, A. S., Sackler, A. M., Johnson, L., and O'Conner, G.: Fed. Proc. 29:778, 1970.

73. Weltman, A. S., Sackler, A. M., Lewis, A. S. and Johnson, L.: Physiol. & Behavior 5:17, 1970.

74. Weltman, A. S. and Sackler, A. M.: Acta Endocrinologica 64:347, 1970.

75. Sackler, A. M. and Weltman, A. S.: Experientia 26:369, 1970.

76. Baer, L., Knowlton, A. and Laragh, J. H.: In "Spontaneous Hypertension, It's Pathogenesis and Complications" edited by Okamoto, K., Springer-Verlag, New York, 1972, page 203.

77. Rappaport, F., Fischl, J. and Pinto, N.: Clin. Chem. 6:16, 1960.

78. Manual of Oxford Laboratories; Procedure for determination of free catecholamines in urine.

79. Purves, H. D. and Sirett, N. E.: Endocrinology 77:366, 1965.

80. Saifer, A. and Gerstenfeld, S.: J. Lab. Clin. Med. 51:448, 1958.

81. Sunderman, W. F.: J. Biol. Chem. 153:139, 1944.

1003541969

Source: https://www.industrydocuments.ucsf.edu/docs/kpvm0000

REFERENCES

82. Baird Atomic Flame Photometer Manual (Model KY-2) Procedure for Serum Sodium and Potassium.

83. Manual of Fluormetric Clinical Procedures, G. K. Turner Assoc. 1966 (2/62). Procedure for Total Serum Cholesterol.

84. Goss, J. E. and Lein, A.: Clin. Chem. 13:36, 1967.

85. Manual of Worthington Biochemical Corp. Procedure for serum total triglycerides and free glycerol.

86. Zilversmit, D. B. and Davis, A. K.: J. Lab. Clin. Med. 35:155, 1950.

87. Vernikos-Danellis, J., Anderson, E. and Trigg, L.: Endocrinol. 79:624, 1966.

88. Vochten, R. F. C., Hoste, J., Delaunois, A. L. and DeSchaepdryver, A. F.: Analytica Chem. Acta. 40:443, 1968.

89. Snedecor, G. W.: Statistical Methods, Iowa State College Press, Ames 1949.

90. Sokabe, H.: Nature 205:90, 1965.

91. Koletsky, S., Shook, P. and Rivera-Velez, J.: Proc. Soc. Exp. Biol. Med. 134:1187, 1970.

92. Koletsky, S., Shook, P. and Rivera, Velez, J.: in "Spontaneous Hypertension: It's Pathogenesis and Complications," edited by Okamoto, K., Springer-Verlag, N. Y., 1972, page 199.

93. Ogino, K., Kira, J. and Matsunago, M.: in "Spontaneous Hypertension: It's Pathogenesis and Complications," edited by Okamoto, K., Springer-Verlag, N. Y., 1972, page 210.

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Item # 10. Space and facilities available

tary needs. Adjacent to the animal room are 2 storage rooms approximately 5'x10' (50 sq. ft.) and 5'x13' (65 sq. ft.). These are used to store food, shavings and other sundry supplies. Also adjacent to the animal quarters is a behavioral study room 7'x12' (84 sq. ft.) used for O_2 consumption, locomotor activity and other studies when required. This room permits animals to be observed and studied in relative quiet. A separate room 10'x17' (170 sq. ft.) removed from the animal room by a corridor and 2 doors serves as office space and area for auditory stress studies. This separation prevents extraneous noise from bells, etc., to reach and disturb animals in the animal quarters. A washroom, approximately 12'x17' (204 sq. ft.) contains an automatic-spray washing machine and sinks which are used to sterilize and cleanse cages and water bottles. The main research laboratory approximately 16'x50' (800 sq. ft.) is provided with desks, table tops, cabinets and much of the equipment cited above. This room contains 3 water-sinks and is the area where autopsies, hematological, histological, and biochemical tests are performed and where calculations are done.

b) Institute of Pathology
Downstate Medical Center, S. U. N. Y.
450 Clarkson Avenue
Brooklyn, N. Y.

At the Institute of Pathology, laboratory rooms and equipment are available for sectioning and automatic fixing and staining of the preparations and slides. They consist of microtomes, auto-technicons, microscopic equipment, glassware and accessory supplies. An electron microscope and fluorscent apparatus are available if these techniques are needed.

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Item # 13. Publications

For a more complete list of some of the Laboratories 61 publications, see Item #12.

Metabolic and Endocrine Effects of Lysergic Acid Diethylamide (LSD-25) on Male Rats, A. S. Weltman and A. M. Sackler, J. Endocrin. 34:81-90, 1966.

Effects of Levels of Audiogenic-Seizure Susceptibility on Endocrine Function of Rats, A. S. Weltman, A. M. Sackler and H. Owens, Physiology and Behavior 3:281 -284, 1968.

Mescaline Hydrochloride Effects on the Endocrine Activity of Male Albino Mice, A. Stanley Weltman, Arthur M. Sackler and Ralph Schwartz, Experimental Medicine and Surgery 26: No. 4, December 1968.

Pre-maternal Isolation Effects on Behaviour and Endocrine Function of Offspring, A. M. Sackler, A. S. Weltman, R. Schwartz and P. Steinglass, Acta Endocrinologica 62:367-384, 1969.

Metabolism Rate, Biochemical and Endocrine Alterations in Male Whirler Mice, A. S. Weltman, A. M. Sackler, A. S. Lewis and L. Johnson, Physiology and Behavior 5:17-22, 1970.

Metabolic and Endocrine Aspects of the Whirler Mutation in Male Mice, A. S. Weltman and A. M. Sackler, Acta Endocrinologica 64:347-358, 1970.

Effect of Mescaline HCl on Resistance of Male Mice to Histamine Stress, A. S. Weltman, A. M. Sackler and L. Johnson, Journal of Pharmaceutical Sciences 59: 1659-1661, 1970.

Plasma Protein and Free Fatty Acid Levels in Male Whirler Mice, A. S. Weltman, A. M. Sackler and G. O'Connor, Experientia 27:878, 1971.

Nicotine Effects in Spontaneously Hypertensive Rats (SHR), A. S. Weltman, V. Pandhi, S.D. Kraus and L. Johnson, Fed. Proc. 32: No. 3, 806, March 1973.

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Biographical sketches of all principal and professional personnel:

A. STANLEY WELTMAN
Born: REDACTED

1. Education

Brooklyn College, Brooklyn, New York	B.A.	1941	Biology and Chemistry
Columbia University, New York, New York	M.A.	1949	Zoology
University of Missouri, Columbia, Mo.	Ph.D.	1956	Zoology

2. Experience

Institution	Nature	Year
Laboratories for Therapeutic Research, Brooklyn College of Pharmacy	Endocrinological, Physiological & Pharmacological Research	1956 to present
University of Missouri	Graduate Research Assistant (Zoology, Histology, Genetics)	1952-1956
U.S. Army	Medical & Surgical Technician (Anesthetist)	1943-1946
Beltsville Research Center	Endocrine Studies	1942-1943
Fort Totten Hospital, N.Y.	Laboratory Analyses (Hematology, Urine Analyses and Blood Chemistry)	1941

3. Background

Dr. Weltman is a staff member of the Laboratories for Therapeutic Research and Associate Professor of Pharmacology and Research at the Brooklyn College of Pharmacy, Long Island University, Brooklyn, New York 11216, and an Associate Professor of the Graduate Faculties of Long Island University, Brooklyn Center, Zeckendorf Campus, Brooklyn, New York 11201.

Dr. Weltman had been involved in investigations at the Beltsville Research Center, Beltsville, Maryland, of hormone assays of gonadatropins, estrogens, pituitary extracts, etc. The various studies at times involved hypophyectomies, gonadectomies and adrenalectomies of laboratory animals.

Academically, he is presently engaged in physiological, endocrinological, pharmacological and biochemical research. In addition to research he lectures in physiology, zoology and pharmacology and acts as a sponsor for students involved in graduate research programs in Biology. During the years of academic learning, research and teaching at the various institutions as well as experiences in Army Hospitals and Beltsville Research Center, Dept. of Agriculture, he has become knowledgeable in the areas of zoology, physiology, genetics, biochemistry, etc. He has instructed the biologists and staff in the techniques used to measure and calculate locomotor activity, O_2 consumption, audiogenic-seizure susceptibility, white blood cell counts, estrus cycle, autopsy procedures, as well as other techniques to be used in this study. All staff members realize the strict requirements needed in the care and maintenance of animals for proper scientific research. He has instructed and worked with the biochemist in verifying the validity and applicability of the

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biochemical procedures to be utilized in this proposal. In many instances, the various publications include the techniques which have been cited. He spends three hours per week in teaching, instruction and administrative duties.

4. Affiliations

Dr. Weltman is a member of the

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In the past, Dr. Weltman and members of the research team of the Laboratories for Therapeutic Research have published investigations involving tranquilizing agents, hallucinogenic compounds (LSD-25, mescaline), audiogenic-seizure susceptibility, auditory stress, vibration stress and whirler mice, etc. These studies have been concerned with behavioral, biochemical, body growth and endocrinal effects produced by the various pharmacological agents, stress or mutant characteristics. Dr. Weltman has assisted Dr. Shirley D. Kraus periodically in teaching the Physiology course at Brooklyn College of Pharmacy. An integral part of the Physiology Laboratory is devoted to study of the effects of pharmacological agents (i.e., epinephrine and acetycholine) on systolic blood pressure of rats using a Physiograph 6 Model. Representative publications by Dr. Weltman follow:

1. Sackler, A.M., Weltman, A.S. and Sackler, R.R.: Effects of Tranquilizing Agents on the Resistance of Rats to Histamine Stress. Nature 183:896-897, 1959.

2. Jurtshuk, P., Jr., Weltman, A.S. and Sackler, A.M.: Biochemical Responses of Rats to Auditory Stress. Science 129:1424-1425, 1959.

3. Sackler, A.M., Weltman, A.S., Bradshaw, M. and Jurtshuk, P., Jr.: Endocrine Changes Due to Auditory Stress. Acta Endocrinologica 31:405-418, 1959.

4. Sackler, A.M., Weltman, A.S., Bradshaw, M. and Heilman, F.: The Effects of Reserpine on Histamine Tolerance and Endocrine Organs of the Rat. Acta Endocrinologica 34:619-626, 1960.

5. Sackler, A.M., Weltman, A.S. and Jurtshuk, P., Jr.: Endocrine Aspects of Auditory Stress. Aerospace Medicine 31:749-759, 1960.

6. Sackler, A.M., Weltman, A.S. and Jurtshuk, P., Jr.: Effects of Splenectomy on the Resistance of Rats to Histamine Stress. Nature 190:274, 1961.

7. Weltman, A.S., Sackler, A.M. and Gennis, J.: Effects of Handling on Weight Gains and Endocrine Organs in Mature Male Rats. J. Applied Physiology 16:587-588, 1961.

8. Sackler, A.M. and Weltman, A.S.: Endocrine and Behavioral Aspects on Intense Auditory Stress, p. 255-283 in Psychophysiologie, Neuropharmacologie et Biochemie de la Crise Audiogene, Centre National de la Recherche Scientifique, Paris, 1963.

9. Weltman, A.S. and Sackler, A.M.: Effects of Thymectomy on the Resistance of Rats to Drowning and Histamine Stress. Nature 192:460, 1961.

10. Weltman, A.S., Owens, M. and Sackler, A.M.: Effects of Age and Thymectomy on Urinary 17-Ketosteroid Levels in Male Rats. Nature 194:1087-1088, 1962.

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11. Sackler, A.M., Weltman, A.S., Owens, H., Kreger, A.S. and Jacobs, R.: Endocrine Differences of Audiogenic-Seizure Susceptible and Resistant Wistar Rats. Amer. Zool. 2:553, 1962.

12. Sackler, A.M., Weltman, A.S. and Owens, H.: Effects of Lysergic Acid Diethylamide on the Total Leukocytes and Eosinophils of the Female Rat. Nature 199:1194, 1963.

13. Weltman, A.S. and Sackler, A.M.: Effect of Lysergic Acid Diethylamide (LSD-25) on Growth, Metabolism and the Resistance of Male Rats to Histamine Stress. J. Pharm. Sci. 54:1382-1384, 1965.

14. Weltman, A.S. and Sackler, A.M.: Metabolic and Endocrine Effects of Lysergic Acid Diethylamide (LSD-25) on Male Rats. J. Endocrinology 34:81-90, 1966.

15. Sackler, A.M. and Weltman, A.S.: Effects of Vibration on the Endocrine System of Male and Female Rats. Aerospace Med. 37:158-166, 1966.

16. Sackler, A.M., Weltman, A.S. and Owens, H.: Endocrine and Metabolic Effects of Lysergic Acid Diethylamide On Female Rats. Toxicology and Applied Pharm. 9: 324-330, 1966.

17. Weltman, A.S., Sackler, A.M. and Sparber, S.B.: Endocrine, Metabolic and Behavioral Aspects of Isolation Stress on Female Albino Mice, Aerospace Med. 37:804-810, 1966.

18. Weltman, A.S., and Sackler, A.M.: Timidity and Metabolic Elimination Patterns in Audiogenic-Seizure Susceptible & Resistant Female Rats. Experientia 22:627-629, 1966.

19. Weltman, A.S. and Sackler, A.M.: Metabolic and Endocrine Function in Whirler Mice. Proc. Exp. Biol. & Med. 123:58-62, 1966.

20. Sackler, A.M. and Weltman, A.S.: Metabolic and Endocrine Differences between the Mutation Whirler and Normal Female Mice. J. Exp. Zool. 164:133-140, 1967.

21. Sackler, A.M. and Weltman, A.S.: Effects of Isolation Stress on Peripheral Leucocytes of Female Albino Mice. Nature 214:1142-1143, 1967.

22. Sackler, A.M., Weltman, A.S. and Kreger, A.S.: Metabolic and Endocrine Aspects of Audiogenic-Seizure Susceptibility in Female Rats. Exp. Med. & Surg. 24:258-269, 1966.

23. Weltman, A.S., Sackler, A.M., Schwartz, R. and Streman, S.: Effects of Isolation on Maternal Aggressiveness and Body Growth Rates of Offspring. Experientia 23:782, 1967.

24. Weltman, A.S., Sackler, A.M. and Owens, H.: Effects of Levels of Audiogenic-Seizure Susceptibility on Endocrine Function of Rats. Physiology and Behavior 3: 281-284, 1968.

25. Weltman, A.S., Sackler, A.M., Schwartz, R. and Owens, H.: Effects of Isolation Stress on Female Albino Mice. Laboratory Animal Care 18:426-435, 1968.

26. Sackler, A.M., Weltman, A.S., Schwartz, R. and Steinglass, P.: Pre-maternal Isolation Effects on Behaviour and Endocrine Function of Offspring. Acta Endocrinologica 62:367-384, 1969.

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27. Weltman, A.S., Sackler, A.M. and Schwartz, R.: Mescaline Hydrochloride Effects on the Endocrine Activity of Male Albino Mice. Exp. Med. & Surgery 26: 187-197, 1968.

28. Weltman, A.S., Sackler, A.M., Schwartz, R., Johnson, L. and Steinglass, P.: Mescaline HCl: Behavioral, Biochemical and Endocrine Changes in Male Albino Mice. Amer. Zoologist 9:1079, 1969.

29. Weltman, A.S., Sackler, A.M., Johnson, L. and O'Connor, G.: Aspects of Protein, Carbohydrate and Fat Metabolism in Whirler Mice. Fed. Proc. 29:778, 1970.

30. Weltman, A.S., Sackler, A.M., Lewis, A.S. and Johnson, L.: Metabolism Rate, Biochemical and Endocrine Alterations in Male Whirler Mice. Physiology and Behavior 5:17-22, 1970.

31. Weltman, A.S., Sackler, A.M. and Schwartz, R.: Maternal Effects on Behavior and White Blood Cells of Isolated Female Mice. Life Sciences 9:291-300, 1970.

32. Weltman, A.S. and Sackler, A.M.: Metabolic and Endocrine Aspects of the Whirler Mutation in Male Mice. Acta Endocrinologica 64:347-358, 1970.

33. Sackler, A.M. and Weltman, A.S.: Blood Glucose and Liver Glycogen Content in Male Whirler Mice. Experientia 26:369-370, 1970.

34. Weltman, A.S., Sackler, A.M. and Johnson, L.: Effect of Mescaline HCl on Resistance of Male Mice to Histamine Stress. Journal of Pharmaceutical Sciences 59:1659-1661, 1970.

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CURRICULUM VITAE

NAME:	VALENTIN MICHAEL YERMAKOV
HOME ADDRESS & PHONE NO.:	11564 REDACTED
MARITAL STATUS:	REDACTED
PLACE & DATE OF BIRTH:	REDACTED
OFFICE ADDRESS & PHONE NO.:	Institute of Pathology, Autopsy Service Kings County Hospital Center, 451 Clarkson Ave. Brooklyn 3, N.Y. IN 2 4000, Ext. 6658.
PRELIMINARY EDUCATION:	First Russian "Archduke Constantine Constantinovich" Kadet Corps Bela Crkva, Yugoslavia (Equivalent to Real Gymnasium) 1932-1940. Taconic Institute, 1949-50 (American Literature and History).
SUPPLEMENTAL EDUCATION:	City College of New York - 1951 (Bacteriology)
PROFESSIONAL EDUCATION:	University of Belgrade, Yugoslavia - 1940-1941. UNRRA University, Munich, Germany - 1945-1946 Rupert Carola University, Heidelberg, Germany - 1946-1949, 1952-1953.
PROFESSIONAL DEGREES:	Physician - Rupert Carola University - 1953 Doctor of Medicine - Rupert Carola University - 1953.
HOSPITAL TRAINING:	Rotating Internship, St. Clare's Hospital, New York City, 1954-1955. Resident, Pathology, Kings County Hospital Center, Brooklyn, New York, 1955-1956.
TEACHING APPOINTMENTS:	Damon Runyon Cancer Research Fellow at New York State University, Downstate Medical Center - 1956-1957. 1 Instructor in Pathology, College of Medicine, Downstate Medical Center, S.U.N.Y. 1957-1962. 2 Assistant Professor, College of Medicine, Downstate Medical Center, S.U.N.Y. 1962-1968. 3 Associate Professor, College of Medicine, Downstate Medical Center, S.U.N.Y. 1968 -
Hospital Appointments:	1. Resident Pathologist, [illegible] 1961-1962 2. Pathologist " " " " 1962-1970 3 Supervising Pathologist " " " 1970 -

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PUBLICATIONS

1. Fitzgerald, P.J., Li, T.G. and Yermakov, V. A comparison of the mass concentration of normal and carcinoma in situ cell of the human uterine cervix by means of the x-ray contact microradiography technique. X-RAY MICROSCOPY AND MICRORADIOGRAPHY. Ed. Cosslett and Engstrom, pp. 520-530, Academic Press, Inc., N.Y., 1957.

2. Fitzgerald, P.J., Yermakov, V., Sabin, L. and Levine, L. The mass of cancer in situ cells of the human cervix uteri as compared to normal cervical cells. Acta Union Internationale Contre Le Cancer, Vol. XV-N. 2:296-302, 1959.

3. Yermakov, V. and Fitzgerald, P.J. Application of x-ray microradiography in Pathology. Bulletin of the New York Academy of Medicine, Vol. 36:7:478-482, 1960.

4. Lipkin, L.E., Yermakov, V. and Aronson, S.M. Ganglionic intracytoplasmic inclusion bodies: x-ray contact microradiographic and histochemical studies. AMA Arch. of Neur. 2:106, 1960.

5. Minkowitz, S., Soloway, H., Hall, Y.E. and Yermakov, V. Fatal hemorrhagic pancreatitis following chlorothiazide administration in pregnancy. Obst. Gyn. 24:337, 1964.

6. Bolooki, H., Margulies, M., Yermakov, V. and Gliedman, M. Portal hypertension with anomalies of inferior vena cava and hepatic vein. Arch. Surg. 94:267-270, 1967.

7. Coppola, A., Yermakov, V. and Caggiano, V. Pleomorphic lymphoma and gastric adenocarcinoma (collision neoplasm) associated with monoclonal macroglobulinemia and amyloidosis. A case report. Cancer, 23:576-585, 1969.

8. Perez, N., Rosen, Y., Lichtman, H. and Yermakov, V. Granulomatous gastritis of probably tuberculous etiology associated with megaloblastic anemia. Case Report. New York State Journal of Medicine. (In Press).

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MEDICAL SOCIETIES:

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CURRICULUM VITAE

NAME: DR. STEFAN SCHWAN

HOME ADDRESS: REDACTED

PHONE:
SOCIAL SECURITY NUMBER: REDACTED
MARITAL STATUS:

PLACE & DATE OF BIRTH: REDACTED

PELIMINARY EDUCATION:

REDACTED GRAMMER SCHOOL
1940 - 1944

HIGH SCHOOL
REDACTED 1944 - 1945

HIGH SCHOOL
REDACTED HIGH SCHOOL DIPLOMA - 1951

/PROFESSIONAL EDUCATION:

Medical Faculty of the University of Gdansk
1951 - 1957 Physician

From 1956 - 1966 Employed in the Department of Pathology at the University in Gdansk as Assistant Professor.

1962 - Received the scientific degree of Medical Doctor.

1966 - Received the degree of a specialist in Pathology.

TRAINING:

Oncological Department of the Polish Scientific Academy - 1960 - 1964.

Fellowship in the Department of Pathology in the Mary Curie-Sklodowska Oncological Institute in Warsaw - 1963 - 1965.

Since 1967 - Worked in the Department of Pathology in the State Hospital in Gdansk and in the Childrens Surgical Clinic of the University in Gdansk.

From 1970 to 1971 - Worked as a ships surgeon in the Polish Ocean Lines.

1971 - Arrived in West Germany and worked as a Chief of the Department of Pathology and Cytology in the Institute of Microbiology and Clinical Chemistry in Weingarten.

Arrived in the United States on December 15, 1971 on a permanent visa.

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STEFAN SCHWAN, M.D.

PUBLISHED WORKS

1. Research on Anticarcinamatous Substances.I.A number of I-bromo 7 -methoxyacridine and 3-bromo-7-methoxyacridine derivatives. Biological Part.-Polish Pathology (Patologia Polska)1958,9,4,331-343.

2. Properties of the fibrinous membrane produced in Poland.-The Polish Physician Journal (Polski Tygodnik Lekarski) I 59,14,26,I-8.

3. Influence of the somatothropine hormon (STH) on the body weight and tumor growth of mice with transplantable Crocker sarcoma.-The Polish - Physician Journal (Polski Tygodnik Lekarski) 1960,15,9,2-7.

4. The Action of some Acridine Derivatives on the growth of Crocker sarcoma in mice. Polish Medical Science and History October, 1960, 3,4,154-166.

5. Isonicotinic acid Hydrazide (INH) as a carconogenic agent in mice. First Report. Polish Pathology (Patologia Polska) 1961,12,1,53-56.

6. Isonicotinic acid hydrazide (INH) as a carcinogenic agent in mice. Second Report. Polish Pathology (Patologia Polska) 1962,13,2,185-194.

7. Influence of hormones of the suprarenal cortex on the transplantable Crocker sarcoma. Societas Scientarum Gedanensis. Acta Biologica et Medica. 1962,II,341-363.

8. Haemanagiomatosis diffusa hepatis with thrombocytopoenia. - The Archiv of Polish Internal Medicine (Polskie Archiwum Medycyny Wewnetrznej) 1964,34,6,781-784.

9. Heart failure due to leukemic infiltration of the heart in a patient with myelosis leukemia.-The Archiv of Polish Internal Medicine (Polskie Archiwum Medycyny Wewnetrznej) 1964,34,II,1399-1492.

10. Two cases of giant hypertrophy of the gastric mucosal rugae (Menetriors Disease). Polish Review -f Radiology and Nuclear Medicine (Polski Archiwum Radiologii i Medycyny Nuklearnej) 1965,29,2,149-156.

11. Rheumatic pneumonia im a six year old child.-Polish Pathology (Patologia Polska) 1965,16,3,367-371.

12. Isonicotinic acid hydrazide (INH) as a cancerogenic factor.III Report.- Polish Pathology (Patologia Polska) 1967,28,2,295-300.

13. The comparying of the clinical and histopathological picture in Hirschprungs Disease. - Memorial of the 44 Polish Surgeons Congress in Krakow (Pamietnik 44 zjazdu Chirurgow Polskich w Krakowie) 26-28.9.1968,440-441.

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NICOTINE EFFECTS IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR).

A.S. Weltman, V Pandhi*, S D. Kraus and L. Johnson*. Labs. Therapeutic Res., Brooklyn Col. of Pharmacy, Long Island Univ., Brooklyn, N.Y. 11216

The effects of nicotine in mature male SHR after a single s.c. dose and after 6 wks of oral intake were noted. In the acute study, rats were sacrificed 30 min. after injections of 0.5 or 1.0 mg/kg of nicotine or saline. The 1.0 mg/kg dose caused significant increases in plasma corticosterone. Signif. depletions were found in adrenal corticosterone and epinephrine along with elevations in plasma FFA. The 0.5 mg/kg dose caused smaller, non-significant changes. No signif. changes in plasma Na, K or cholesterol levels were found with either dose. In the subacute study, test rats were given 2.2 mg/kg of nicotine orally in water per day for 6 wks. This represents a "two-pack-a-day" dose of nicotine. A transient increase in systolic b p taken at 24 hrs. was signif. Increases observed after the 1st and 2nd wks. were not signif., nor were decreases at the 4th and 6th wks. During the first 5 wks., the test rats had significantly lower body wts. than controls but the differences became gradually less. At the 6th wk, there was no signif. diff. between the 2 groups. At sacrifice, plasma cholesterol levels were significantly lower in the test rats but there were no signif. differences in other biochemical analyses or organ wts (liver, thymus, adrenals, testes, kidneys, heart, etc.). By the 6th wk, the test rats appeared to accommodate to nicotine. (Supported in part by CTR Grant 833)

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